The Exposome and Asthma

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KEYWORDS

• Asthma • Exposome • Allergen • Air pollution • Climate change

KEY POINTS

- The environment to which the individual is exposed (exposome) is continually influencing the pathobiology of asthma.
- Indoor and outdoor environments play a role in pathogenesis via levels and duration of exposure, with genetic susceptibility as a crucial factor that alters the initiation and trajectory of common conditions such as allergies and asthma.
- Knowledge of environmental exposures globally and changes that are occurring is necessary to function effectively as medical professionals and health advocates.

INTRODUCTION

Asthma is a common condition that can affect up to 339 million people, and the prevalence is rising.[1] Despite having common features, individuals diagnosed with asthma may have a unique etiology, symptomatology, and response to therapies, resulting in varying levels of asthma control. Intrinsic and genetic factors play a significant role, as demonstrated by a familial link. In addition, the environment to which the individual is exposed (exposome) is continually influencing the pathobiology of asthma.[2–5] This complex interaction of factors can often make the evolution and pathophysiology of asthma difficult to ascertain and comprehend. Among medical providers, there continues to be an enhanced awareness of environmental factors and how they have an impact on asthma pathogenesis, evolution, symptoms, and long-term morbidity. The exposome concept considers all exposures of an individual in a lifetime and how those exposures relate to health (**Fig. 1**).[6–8] In this context, there are known associations, associations that are not fully established, and exposures that demonstrate more distinctive effects based upon age, chronicity of exposure, and genetic predispositions.[9–11] It is through ongoing research and discourse that one will be able to determine precise treatments for individuals and have a better understanding of environment and exposure (exposome) impacts upon the health of individuals and larger at-risk populations.

This article focuses on the interaction of patients and their environments in various parts of their growth, development, and stages of life. It will discuss exposures from indoor and outdoor environments, consider many possible and probable exposures associated with asthma through a lifetime, and inform the reader how human impact on the environment locally and globally relates to public health, specifically respiratory health.

These topics are presented through the broader intent to support the role of medical professionals as educators and health advocates. Being knowledgeable of environmental exposures globally and changes that are occurring over time is necessary to function effectively in that realm. Ongoing research is revealing specific risks, means to mitigate human impact, and strategies to adapt to environmental changes. Such research and clinical expertise offer opportunities to influence public policy in this regard.[12,13]

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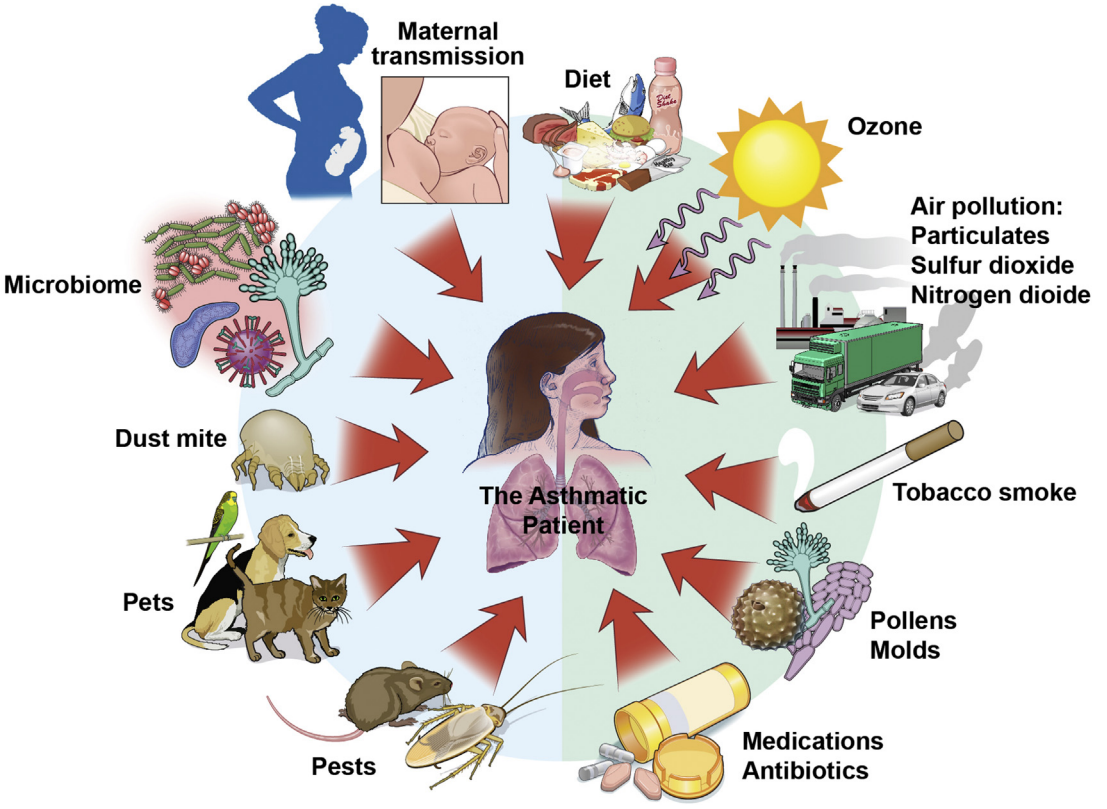

Fig. 1. The exposome concept considers all exposures of an individual in a lifetime and how those exposures relate to health.

PRENATAL AND POSTNATAL

Microbiome – Effect on Prenatal and Early Life Contributing to the Inception of Asthma

External exposures comprising the exposome contribute to the development of asthma, making it a potentially preventable disease process through environmental modifications. Allergic sensitization and respiratory infections with wheezing are independent and synergistic risk factors in the development of asthma. These factors are influenced in early life by the microbiome, which is a potential modifiable exposure in the natural history of asthma. Early microbial exposure and bacterial diversity within the human microbiome have been noted to be crucial elements in the development of innate immunity.[14] Factors associated with urbanization, improved sanitation, and vaccinations have led to decreased microbial exposure in early life and loss of biodiversity in the human microbiome over time. These changes in turn have been associated with increased susceptibility to the development of allergic sensitization and asthma.

Formation of the microbiome begins in utero largely through maternal transmission.[15] Differences in the gut microbiota during infancy with respect to diversity of strains and colonization of specific bacteria are linked with the likelihood of developing atopy. A comparison of diversity in stool flora at age 1 month showed that decreased diversity was predictive of allergic sensitization at age 6 years.[16] Another study revealed that risk of atopic sensitization was inversely related to diversity of infant gut microbiota.[17] Also, in contrast to colonization with *Bacteroides* and *Lactobacillus* species, which have been associated with decreased risk of allergy, specific colonization in the gut with *Clostridia* species was related to wheezing and allergic sensitization.[18]

Microbial colonization of the airways in early life has also been shown to play a role in risk of asthma development. One study showed that colonization with *Streptococcus* species in early life (age 2 months) was associated with chronic wheezing at age 5 years.[19] Another analysis of airway bacterial colonization in asymptomatic neonates at 1 month of age revealed that early colonization with *S pneumoniae, Haemophilus influenza,* and/or *Mycobacterium catarrhalis* was associated with recurrent wheeze by age 5 years.[20] Antibiotic use in infancy was associated with

decreased abundance of *Bifidobacterium* and *Bacteroides* species.[21]

Given the compelling role of the microbiome in early life and development of asthma, it is important to understand the factors that can affect bacterial colonization and formation of the microbiome. Nutrition, medication use, environment (ie, farm exposures) and mode of delivery have all been demonstrated to have influences on the early life microbiome. Breastfeeding has been shown to alter the airway microbiome toward a more protective profile[22] and greater bacterial diversity.[3] Frequency of maternal urinary tract infections (use of maternal antibiotics) and infant antibiotic use in the first year of life were associated with increased risk of childhood asthma in a dose-dependent proportion.[23]

The benefit of bacterial diversity exposure in early life has been demonstrated through several human studies comparing children living in farm environments versus children living in urban environments. Children who lived on farms had increased indoor microbial exposure as well as more diversity within the microbial environment. These children also had less asthma and atopy compared with peers not living on farms.[14] Increased microbial diversity in the farm environment has been shown to be inversely associated with risk of asthma.[24] In a study comparing children of similar genetic ancestry living in traditional farming environment versus industrial farming, the prevalence of asthma was noted to be 4 to 6 times lower in the children living in the traditional farming environment (Amish community).[25] A proposed mechanism is the protective role of endotoxin, a component of gram-negative bacterial cell walls and a marker of microbial exposure. Amish homes contained higher levels of endotoxin in house dust. This finding is supported by a separate study where higher levels of endotoxin in child mattresses were associated with reduced risk of allergic sensitization and atopic asthma.[26]

Household/Indoor Exposures of Allergens

Indoor particulate matter (PM), including allergens and chemical pollutants, is a major factor in the propagation of asthma worldwide. The specific culprits of reduced indoor air quality vary greatly across countries, with differences influenced by climate, urbanization, and socioeconomic level. Developing countries bear a larger burden from indoor PM pollution because of the use of biomass fuel combustion. Geographic influences can be seen in colder climates where more time may be spent indoors. In the United States, the Environmental Protection Agency estimates most individuals spend approximately 93% of their time indoors.[27]

The relevant allergens in the indoor environment include house dust mites, cockroaches, molds, rodents, and pets. Sensitization in early life (before age 3 years) and multiple allergen sensitization are risk factors for the development of asthma that can persist through adulthood.[28] Perennial allergen sensitization has been linked with increased severity of asthma. Sensitization and exposure to these indoor allergens has been shown to contribute to asthma morbidity as measured by number of asthma exacerbations, days lost from school and work, hospital/emergency room visits, severity of asthma, and medication use.[29,30] In modern society, the efforts to make more energy-efficient homes and desire for comfort indoors (ie, increased indoor temperature, increased humidity, use of carpeting) all contribute to escalating the risk of poor indoor air quality by encouraging proliferation of allergens.

The most effective interventions in modifying indoor allergen exposure have used a multifaceted approach involving patient education, targeted remediation (ie, pest control, impermeable bed covers), and in-home visits/assessments.[31,32] As health care models shift toward value-based care, the use of effective environmental interventions may be increasingly desirable for decreasing asthma morbidity. Using environmental interventions to reduce allergen/irritant exposures can lessen reliance on medications and health care utilization, which will ultimately result in cost-effective and sustainable changes.

House dust mites

House dust mites (HDMs) are ubiquitous microscopic organisms found inside dwellings year-round. HDM sensitization is noted worldwide, with a higher prevalence among individuals with asthma compared with the general population. Asthmatics with HDM sensitization have increased risk for asthma morbidity as measured by health care utilization and increased medication use.[33]

The allergenic proteins of HDM are found in the gut and feces of the organism which contribute to both sensitization and clinical symptoms of the respiratory tract with ongoing exposure. HDMs thrive indoors with increased humidity and elevated temperatures. They feed off human skin cells and are found in high concentrations in bedding (pillows, mattress), carpeting, rugs, stuffed animals, and any item with padding. Interventions to reduce exposure to dust mites are geared toward removal as well as creating barriers: encasing any padded items in impermeable covers, removing likely reservoirs, frequent vacuuming, washing and drying

bedding in high heat weekly, maintaining humidity less than 50%, and avoiding carpeted flooring, stuffed animals, and upholstered furniture. Studies evaluating the clinical effect of avoidance measures have shown varying degrees of improvement. The greatest impact is seen in children, where a single intervention of using mite-impermeable bed encasings correlated with reduced rate of hospital visits for asthma exacerbations.[34]

Another potential route of sensitization that has been proposed is oral sensitization to dust mite allergen through breastmilk. A study found the presence of dust mite allergen in breast milk correlating with risk of atopy and asthma at 5 years of age.[35] There was a higher risk in mothers with asthma and allergy themselves, suggesting that a combination of environmental factors and genetics plays a role in the development of asthma.[35] Further studies are needed to investigate the correlation with oral sensitization, as the implications could help shape guidelines for environmental avoidance measures in prenatal and early life.

Pets

Keeping domestic animals, typically cats and dogs, in the home is a common practice in many countries. It is estimated that in the United States over 50% of families are pet owners.[36] Cats are generally more allergenic than dogs; however, both can cause allergy from proteins found in the dander, saliva, and urine. The major allergenic protein of cats (Fel d 1) is small in size, lending this allergen to stay airborne and also easily stick to surfaces and clothing. Indoor exposure to animal allergen occurs inside homes as well as indoor commercial spaces, schools, and work places. This is highlighted by the fact that cat and dog allergenic proteins have been found in house dust from places where there are no animals.[37] The rate of sensitization to domestic animals appears to be rising in the United States and European countries.[38] Exposure to animal allergen in asthmatics who are sensitized is associated with significant asthma morbidity and increased health care utilization.[39]

The most effective remediation for animal allergens is removing pets from the home; yet studies show it can take up to 6 months to eliminate detectable allergen in the home after animal removal.[40] Eliminating animal allergen in the home has been shown to improve asthma symptoms for individuals in the home. Studies evaluating other mitigating measures including a combination of washing the cat weekly, reducing furnishings, vacuum cleaning, and air filtration have shown variable impact on control of asthma symptoms.

The relationship between early exposure to animal allergen and development of sensitization and asthma is more complicated. Some studies have shown early exposure to dogs having a protective effect against allergies. It is postulated that this may be in part caused by the effect of dogs on the home microbiome and in turn microbial exposure in early life. The relationship of sensitization with early exposure to cat on the other hand has not shown consistent patterns, and in some studies has noted an increased risk for sensitization. The link between allergen exposure and sensitization in early life seems to be influenced by timing, environmental factors, and epigenetics. This is an area in which further research may be helpful in elucidating clear guidelines on whether modifying animal exposure in the home can change risk of asthma development.

Mold

Mold spores are ubiquitous in indoor and outdoor environments. There are more than 100,000 known mold species, of which at least 80 have been identified in indoor dwellings.[41] Spores can be small, and, in some cases, microscopic, allowing them to enter deep into the airways. Mold spores thrive in high levels of humidity and are found indoors as result of excessive moisture from water intrusion, inadequate ventilation, defective plumbing, or other structural problems. Indoor mold exposure can be a potential asthma trigger in homes as well as public indoor environments such as schools and places of work. There is a well-established link between sensitization to mold and presence of asthma in adults and children, and early exposure to mold or dampness in infancy has been associated with increased risk of asthma.[42–44] Mold sensitization and exposure are associated with asthma morbidity. Indoor dampness, linked with mold exposure, has been shown to increase the risk of poor asthma control, asthma exacerbations, and increased health care utilization.[45,46]

Indoor exposure to mold may be more prevalent among lower socioeconomic levels because of the higher costs associated with remediation. There is some evidence that mold remediation interventions (eg, removal of visible mold, decreasing humidity in damp basements, repairing leaks, and removal of water-damaged materials) can have impact on individuals with asthma with reduction in emergency room visits and hospitalizations due to asthma. However, some studies have shown no effect; therefore further study with larger sample sizes may be helpful in clarifying benefit of mold remediation efforts.

Cockroach

Cockroaches are a significant source of indoor allergen exposure; infestation is more common in

urban environments with dense populations and linked with low socioeconomic status. The allergenic proteins are found in saliva, secretions, debris, and fecal material. Sensitization to cockroach varies across communities and has been found to be has high as 60% to 80% of children in low-income urban environments.[29,30] Cockroach sensitization and exposure have been associated with increases in asthma morbidity, severe asthma, and health care utilization, particularly in low-income inner-city populations.[47]

Interventions to eliminate cockroaches have been effective in reducing cockroach exposure and asthma symptoms. Integrated approaches appear most effective and include professional extermination using insecticide, use of roach traps, putting all food in sealed containers, plugging holes, keeping kitchens clean, promptly washing dishes, frequent disposal of garbage, and directed education on these avoidance measures.

The role of cockroach allergen sensitization in development of asthma is not clear. However, the known association with asthma morbidity and disproportionate burden of exposure in children of lower socioeconomic status have implications of impacting health care utilization well into adult hood.

Rodents

Rodents, including mice, rats, and guinea pigs, are a common source of indoor allergens in inner-city and urban dwellings. These are relevant allergens in homes, public buildings such as schools, and occupational exposure in laboratory facilities using mice for research. The exposure in homes varies greatly depending on geography and urban/rural setting. In certain locations, rodents have been found to be nearly ubiquitous, with mouse protein noted in house dust of the majority of homes in a community. The allergenic protein can be found in urine, skin cells, and hair follicles. Sensitization to mouse and allergen exposure is associated with asthma morbidity and appears to be dose-dependent.[48,49]

Risk factors for higher concentration of mouse allergen in a home include presence of holes or cracks in the wall or doors, reports of mouse sightings, and presence of cockroaches.

Integrated pest management is a remediation approach that has been shown to effectively reduce allergen level in the home. It is a multifaceted plan including vacuuming, using low-toxicity pesticides, placing traps, and sealing holes.[50] This has been shown to reduce allergen levels and in some studies improve health outcomes, reduce health care utilization, and reduce missed days of school for individuals with asthma.[51,52]

Environmental tobacco smoke

Environmental tobacco smoke (ETS) is smoke released into the air from burning cigarette, cigar, or pipes. This contaminates indoor air in homes and common spaces, causing increased asthma morbidity.[53] Exposure to ETS in utero and in early life has been linked with development of asthma and atopy.[54,55] Residue from tobacco smoke, referred to as thirdhand smoke (THS), can persist for weeks to months by sticking to surfaces and dust after smoke is gone. The residue is comprised of chemicals that can react to other air pollutants, creating toxic particles. Young children who are crawling are at risk for exposure by ingesting particles residing on surfaces such as floors, walls, and furniture. A large study of a well-characterized cohort demonstrated that THS exposure was associated with poor asthma control, decreased quality of life, and lower lung function. Often the level of asthma severity was dependent solely on exposure to THS, converting nonsevere asthma to severe asthma. The relation also appeared to be related to genetic antioxidant capability.[56]

Although smoking cessation is the ideal remediation strategy, this has not been shown to be an effective intervention as it as depends on the cooperation of the smoking household members. The use of HEPA air purifiers can be helpful in reducing airborne particles and reducing asthma morbidity as measured by health care utilization in individuals with asthma who cannot avoid ETS.[57] Smoking outside the home may not be an effective mitigating strategy in young children because of the risk of thirdhand smoke (THS).[58]

Indoor chemical pollutants

Nitrogen dioxide Nitrogen dioxide is an important component of indoor air pollutants. It is produced from high-temperature combustion and accumulates in the indoor atmosphere with unvented combustion processes most commonly from gas stoves, kerosene heaters, and poorly vented furnaces and fireplaces. Elevated nitrogen dioxide levels in homes, even below the EPA outdoor standard (53 ppb) has been associated with increased symptoms and use of rescue medications in children with asthma.[59] Interventions such as replacing existing gas stoves with electric stoves, installing ventilation hoods over existing gas stoves, and using air purifiers with HEPA and carbon filters have been shown to be effective in reducing indoor nitric oxide levels. Indoor air quality is also significantly related not only to smoking and cleaning products, but also from using a fireplace or cooking. Cooking may actually increase particulate matter concentration by 1.5- to 27-fold.[60]

Volatile organic compounds Volatile organic compounds (VOCs) are often from human/anthropogenic sources including construction materials, formaldehyde in particle board, oil-based paints, printer toner, fragrant decorations, and indoor plants.[61]

Endotoxin

Endotoxin is a component of the outer membrane of gram-negative bacteria. It is associated with the presence of dampness, mold, pets, or rodents in homes. Endotoxin has been implicated in a variety of toxic effects including airway inflammation and airflow obstruction and therefore an interesting target for indoor air quality improvements. Elevated levels of endotoxin are relevant in the home, school, and workplace for certain occupations. Endotoxin exposure in an inner-city community was positively associated with wheeze at 2 years of age, and personal endotoxin exposure has been associated with increased asthma symptoms and decreased forced expiratory volume in 1 second (FEV_1).[28,62] Occupations in agricultural industry and farming have higher exposure to endotoxin through work, which has been associated with acute and chronic respiratory disease.[63,64] Further study is needed to elucidate the effect of endotoxin exposure on asthma and utility of remediation measures to reduce endotoxin levels.

As described previously, there are a multitude of sources and types of indoor air pollution that affect asthma. In the next sections, relationships of indoor-to-outdoor and primarily global outdoor pollutants will be discussed.

RELATION OF INDOOR AND OUTDOOR AIR QUALITY

Poor or suboptimal indoor air quality is influenced by many sources (eg, mold, pets, dust mites, and chemicals) and can have an adverse effect upon respiratory conditions. This is notable, because most people spend more than 90% of their time indoors.[27] However, indoor environments are not an isolated environment system, and outdoor air quality affects indoor spaces.[65] These correlations vary based upon ventilation, circulation of air indoors, pollution levels outside the housing envelope, and meterological conditions.[27,66] Air exchange rates of 0.35 per hour are recommended in order for the actual amount of air changed to be 63.2% in 1 hour. However, these guidelines may need to be modified based on factors such as outdoor air pollution and number of people occupying the home (eg, more than 15 cubic feet per meter per person).[65,67]

Various factors affect this relationship.[68] Particulate matter levels depend on baseline indoor particulate matter, and are increased by cooking (grilling or frying), exhaust from burners, tobacco smoking, and increased foot traffic. Air circulation and ventilation of the indoor-outdoor environment affect total levels. Particulate matter levels indoors depend largely upon velocity of air movement. Some pollutant such as nitrogen dioxide and other byproducts of VOCs linger until they become diluted or dissociate into radicals and nitrogen dioxide. In addition to air conditioning, appropriate exchange rates, smoke-free homes, maintaining allergen protective measures, and removing or wiping shoes at entrances can reduce indoor particulate matter levels.[68]

Three mechanisms allow outdoor air to enter and affect indoor environments, including mechanical ventilation (via intake for air conditioning and HVAC systems), natural ventilation from outdoor airflow, and infiltration through poorly sealed areas of the housing envelope.[69] Importantly, as changes in the outdoor environment occur, indoor exposures will also change. For example, more than 75% of daily indoor variations of particle and black smoke can be explained by daily outdoor variations.[70] Indoor to outdoor ratios of nitrogen oxides (NOx) vary from 0.5 to 1 with little effect on building permeability while ratios of ozone vary from 0 to 0.5 with building permeability being a significant factor.[71,72] Therefore, the indoor-outdoor relationship of air quality depends upon sources in either compartment, the exchange factors, and attempts to control the sources in each sector.

OUTDOOR EXPOSURES

Pollen

Windborne pollen is a major contributor to allergic asthma. Pollen grains from trees, grass, and weeds are transmitted by the wind and can cause upper and lower respiratory symptoms through immunoglobulin E (IgE)-mediated hypersensitivity reactions on mucosal surfaces. The degree of clinical reaction to pollen depends on the amount of pollen dispersed by a plant, the duration of exposure, and the allergenicity of the pollen. Certain plants may be more influential due to these factors, such as the ragweed plant, which is known to produce over 1 billion pollen grains in 1 allergy season.[73]

The effect of pollen allergy is seen worldwide and most prominent in temperate regions. Depending upon the geographic location, there may be distinct seasons for different types of pollen. For example, in North America, tree pollen exposure is in the spring, grass pollen in the summer, and weeds and ragweed in the fall. Exposure to airborne pollen is linked to increased asthma

morbidity, as a study New York showed emergency room visits for asthma attacks, particularly in children, were associated with peaks in tree pollen levels.[74]

Outdoor Air Pollution

Air pollution is a varied mix of components dependent upon industrial and traffic-related emissions and geographic factors such as mountains and valleys. In addition, weather factors such as rainfall, wind speed, and temperature play a role. Mechanisms of air pollution-related compromise to lung health occur via increased permeability of bronchial epithelia, affecting clearance and protection of the airway from allergens and irritants. Environment can also affect respiratory health via epigenetic processes, including by regulation of chromatin, which is one's gene expression profile. DNA methylation and histone modifications are dynamic processes that have been shown to be altered by the external environment. Genes may also be modulated by changes in microRNA expression.[4,7,75] These epigenetic phenomena in which genes may respond to environmental influences explain the gene and environment interactions for disease occurrence and amplification.[4,7]

Air pollution is often related to combustion processes, which also contribute to greenhouse gas emissions.[13] This perpetuates the cyclical issue of air pollution. Methods to evaluate modes of air quality-related lung health have been varied. These include large national health databases, prospective cohort studies, panel studies, and more recently cohort studies in collaboration with more specific air quality monitoring and respiratory-related health markers.[76–79] Outdoor pollutants such as ozone, particulate matter, sulfur dioxide, and nitrogen dioxide are well known to trigger asthma exacerbations and have been associated with reductions in the rate of lung development.[80] Sources include motor vehicle traffic, industrial sources such as petrochemical plants, or coal-fired power plants.[81–83] Another factor that affects the health associations with air quality is the various sources (steel mills), species (organic or inorganic), and components (diesel with adherent pollen grains) of air pollution.[84–86]

Ozone

In contrast to stratospheric ozone levels that protect the earth's atmosphere from 6 to 30 miles above the earth's surface, ambient ozone is present at the respirable ground level closer to the earth's surface. This ambient ozone poses health risks, particularly for those with chronic pulmonary conditions. Ozone is comprised of 3 molecules of oxygen O_3 formed from an oxidative reaction in the presence of pollutants in the atmosphere (eg, VOCs and NOx), heat, and sunlight. Substrate chemicals are released from sources such as burning of fossil fuels, motor vehicle exhaust, and emissions from industrial facilities where molecular oxygen has added oxygen radical, and O_3 is formed. Ozone is therefore a seasonal pollutant that builds up over the course of the day, and in North America, high ozone season occurs from May to September.[87]

Effects of ozone on respiratory conditions include worsening susceptibility to allergens. Summer ozone levels affect respiratory allergy and hay fever symptoms, even when stratified by urban versus rural status.[88–91] Ozone effects are higher after a lag period 24 to 48 hours after exposures, as there is a priming effect to enhance the inflammatory effect of allergen exposures. This lag effect may account for people's inability to perceive the association. Exposure to higher ambient ozone levels has been related to eosinophilia in airways, reducing in small airway airflows FEF25 to 75.[78] Further, ambient ozone levels have been shown not only to worsen existing disease but also with incidence of asthma.[92] The Children's Health study found that children playing 3 or more sports during high ozone days were more likely to have newly diagnosed asthma. Children are particularly sensitive/susceptible to ozone and experience more asthma symptoms, emergency department visits, and intensive care unit admissions.[75,93,94] Children may be also more predisposed because of lungs that are in growth phase, have higher minute ventilation, and more time spent outdoors during summer.

The pathophysiology of these associations may be caused by inflammation, oxidative stress including from increased NADPH oxidase activity, or enhanced allergenic stimulation/eosinophilia.[95] Higher ambient ozone exposures have been temporally associated with higher IgE levels and peripheral eosinophilia[82,96,97] and present oxidant stress to the airways.[98] Exhaled nitric oxide has been shown to correlate with higher ozone levels, indicating increased allergic airway inflammation in patients with asthma.[78,91] Molecular mechanisms may be varied; however, there is evidence of cells' ability to change their behaviors due to environmental exposures (also called plasticity) in cell phenotypes.[75]

Particulate Matter

Particle matter is a year-round pollutant, comprised of a mixture of suspended solids and liquids in the air categorized based upon size.

The particles are produced from industrial, traffic, and geological sources (dust from roads or via chemical reactions in the atmosphere caused by released chemicals from motor vehicles or industrial sources). PM is not visible. Coarse particles (PM10) are 2.5 to 10 um in diameter and fine particles (PM 2.5) are 2.5 um in diameter or less and released from combustion. Although PM is formed in the presence of incomplete combustion of fossil fuels, it can further combine with organic material such as pollen, endotoxins, and fungal spores, creating the immunomodulating and inflammatory responses related to asthma.[27] PM size is related to its potential health effects, as transit in the airways, and absorption/inflammation, are related to particle size and the efficiency of airway defense mechanisms. Inhalable particulate matter that can reach the lower airways includes PM10, PM2.5, and ultrafine (<1 um) particulate matter. PM 2.5, because of its smaller size, is thought to possess a greater health risk due to being able to be inhaled more deeply into the lungs. PM larger than 5 um and less than 10 um may only reach the proximal airways and be expelled by mucociliary clearance. Fine PM is able to transit to the alveolar level and cause inflammatory responses through mediator release more systemically, predisposing to respiratory and cardiac diseases.[99–101]

PM has been associated with the exacerbation of respiratory illnesses. Proximity of homes to major roadways and highways is associated with increased asthma symptoms, emergency department visits, and hospitalizations.[77,100,101] Children who lived within 150 meters of nearest freeway had more deficits in lung function, which been associated with NOx pollutants.[100] Morbidity from chronic asthma and chronic obstructive pulmonary disease (COPD) had consistent associations with PM pollution.[102] These associations are likely caused by the increased inflammatory processes from inhalation with irritation of airways, oxidative stress with formation of inflammatory markers, and mitochondrial dysfunction.[103,104] By promoting release of specific cytokines, chemokines, immunoglobulins, and oxidants in the upper and lower airway, symptoms appear from inflammatory cascade, resulting in increased mucus secretion and bronchial hyperresponsiveness.[103] As demonstrated in the Hyde Park study, which compared exposure to high traffic pollution (Oxford Street) to lower pollution (Hyde Park), airway acidification and sputum myeloperoxidase concentration at 24 hours was higher after exposure on Oxford Street. These inflammatory markers are higher even in instances with relatively modest reductions in lung function, demonstrating the mechanisms by which traffic-related air pollution may affect individuals with asthma.[79] Particles are inhaled, and, depending upon the size and components from the region adherent to molecule (allergens or LPS from bacterial cell walls), airway inflammation may then occur.[89,105]

Diesel exhaust particles (DEPs) and their components such as polycyclic aromatic hydrocarbons make up the majority of particulate matter pollution in urban areas. PM sizes are fine and ultrafine; however, they can coalesce and have other particles adhere to the vehicle provided. The hydrophobic nature of DEPs allow deposition onto the mucosa and not only causes immediate irritant effects but also more chronic symptoms over time such as cough, production of sputum, and diminished lung function. DEPs can enhance the allergenicity of aeroallergens, rendering atopic subjects more susceptible through synergistic expression of allergen-specific IgE and Th2 cytokines.[106,107] In addition, modifications of genetic signaling have been thought to be a mechanism of gene-environment interplay with air pollution and asthma pathogenesis.[75]

Traffic-related air pollution (also known as TRAP), a combination of particulate matter, nitrogen dioxide, and suspended road dust, has been consistent as a trigger for patients with asthma.[80] Traffic-related air pollution affects not only asthma but also COPD, suggesting an even longer-term effect.[108] TRAP and PM in general also affect other chronic conditions. Cardiovascular diseases are also increased and have increased mortality and morbidity from PM.[13]

Nitrogen Dioxide

Nitrogen dioxide is a precursor of ozone, which is formed with additive presence of heat and sunlight. The predominant source of nitrogen dioxide is automobile exhaust, followed by power plants and other industries that burn fossil fuels.[27] However, there are some studies that demonstrate that acute exposure to nitrogen dioxide is associated with asthma and rhinitis and decrement in lung function in individuals with asthma part of TRAP, as in conjunction with black carbon and particulate matter, is the mixture related to TRAP. Growth of lung function is impaired in children with chronic exposure to traffic-related pollutants such as nitrogen dioxide.[109,110]

Sulfur Dioxide

Sulfur dioxide can be a pulmonary irritant and results in increased bronchial responsiveness and bronchomotor tone in patients with asthma.[111,112] Formed from industrial pollutants, sulfur dioxide is a year-round substance in the air formed with the

burning of fossil fuels that contain sulfur. In contrast to ozone, where there are more lingering and lag effects of asthma-related symptoms, sulfur dioxide-related symptoms are more short term, during periods of exercise and high ventilatory rates, and may be related to cholinergic-mediated neural mechanisms.[13] However, sulfur dioxide is felt to be more deleterious in combination with other pollutants than as a single agent of concern. These associations were noted during the Beijing Olympics. When industrial pollutant sources were curbed around the times of the games and resulted in lower sulfur dioxide levels, public health metrics related to exacerbations of asthma were reduced.[113,114]

HOW CLIMATE AFFECTS AIR POLLUTANTS AND ENVIRONMENTAL TRIGGERS FOR ASTHMA

Greenhouse gas emissions and carbon pollution contribute to increases in temperature in the atmosphere.[13] Climate change is caused by increases in global surface temperatures from greenhouse gases in the troposphere that reflect back infrared radiation to the earth's surface.[12] These greenhouse gases include predominantly carbon dioxide and also methane, nitrous oxide, black carbon, ozone, and various hydrofluorocarbons in the atmosphere. The heat-trapping nature of carbon dioxide is what provides the greenhouse effect and promotes enhanced warming of the earth's surface.[115] Approximately half of total carbon dioxide increase in the earth's atmosphere has occurred in the last 40 years; this phenomenon was recognized as early as the 1800s.[116]

During the American Thoracic Society International Conference in 2010, clinical researchers and scientists authored a consensus statement on climate change and health.[12] There was agreement that the most serious health risks include heat-related illness from heat waves and increased air pollution, but also from desertification, which poses particular risks to pulmonary health (asthma and COPD) from increases in air pollution and particulate matter exposure.

Heat Illnesses/Extreme Temperatures

Heat waves are defined as daily maximum temperature of more than 5 consecutive days exceeding the average max temp by 5°, compared with reference normal period between 1960 and 1990 according to the World Meterological Organization.[117,118] Health is affected by climate change in direct and indirect ways. Directly, changes in temperature produce sources of stress for chronic diseases. Indirectly, with heat as a precursor of many pollutants (particulate matter and ozone), higher levels of air pollutants potentiate the inherent risk of air pollutants and airway inflammation in asthma. Increased desertification and dust storms create increased inflammation in airways.[86,115,119] With respect to ozone and climate, more warm days with higher surface temperatures and continued burning of fossil fuels allow buildup of VOCs as a substrate in the natural chemical reaction to produce more ground level ozone. This occurs without increased substrate; thus higher temperatures alone prolong peak episodes of ambient ozone.

Air Pollution

Various air quality simulations demonstrate that climate-induced increases in ozone lead to adverse health impacts, suggesting that 50% to 90% of the United States will be exposed to increased levels of ozone exposure.[120] However, in combination with other pollutants such as particulate matter and TRAP, the estimated ozone-related health effects will likely be amplified.[121] With particulate matter, traffic in colder climates, and stagnation with weather patterns, it has been suggested that the global population-weighted PM 2.5 exposure has already increased by 11.2% since 1990.[6,13,118] Estimated projections of the future suggest that 130 million people (half of the global population) will have allergic disease by 2050.[13] Certain patterns have already been noted. Areas with lower temperatures and pollen counts have lower prevalence of allergy, while extreme dry environments with sunlight combining with high pollen counts result in higher prevalence of allergy.[122,123] With changes in climate, earlier flowering has been seen from ragweed pollen as well as from birch, oak, and olive trees. Longer seasons are likely also supplemented by the enhanced allergen content of pollen caused by the altered ecosystem. However, it should be noted that this molecular aerobiology evidence is still in its infancy.[11]

Pollen

The gradual temperature warming associated with climate change has had a major impact on air quality with respect to pollen through its influence on the length of pollen seasons, amount of pollen produced, and the allergenicity and distribution of pollen spores. These influences are seen in emerging patterns, where regions with lower temperature and pollen counts have relatively lower prevalence of allergy, and areas with warmer temperature and dryer environments, conducive to spread of windborne pollen, have higher prevalence of allergy.[122]

Rising temperatures have been associated with longer pollen seasons, with the greatest impact

seen in higher latitudes. In North America for example, since 1995 the ragweed season has lengthened from 13 to 27 days.[124] With longer pollen seasons, allergenic plants such as ragweed can grow bigger and produce more pollen over time, leading to increased seasonal asthma morbidity.

In laboratory studies, the size of a ragweed plant and amount of pollen produced were shown to increase with higher levels of carbon dioxide exposure; this showed that as a product of fossil fuel combustion, carbon dioxide is a powerful food for allergenic plants.[125] This has also been demonstrated with timothy grass pollen, where exposure to higher levels of carbon dioxide show approximately doubling of pollen production.[126] Examining this relationship in a natural environment showed a similar association; ragweed plants planted in an urban Baltimore grew faster, flowered earlier, and produced more pollen than plants grown outside the city.[127] Living in proximity to heavy traffic areas is associated with increased pollen-induced respiratory symptoms.[86]

Urbanization is associated with higher traffic patterns and industrial emissions. creating a significant difference in air quality and PM compared with rural environments. The prevalence of paved and dark surface roads, buildings, and open lots increases heat absorption and leads to higher temperatures in the urban environment.[128] This has been referred to as the urban heat island effect, which subsequently leads to acceleration in pollen production and air pollution.

The rise in carbon dioxide levels associated with climate change has driven an increase in air pollutants, which in turn interact with pollen to increase allergen particles and allergenicity. Several mechanisms have been identified, including direct damage of pollen cell wall facilitating allergen release, stimulation of specific allergen production in pollen grains, and acting as an adjuvant by carrying small allergen particles through the airways. The mechanism of increasing allergen protein within the pollen has not been well studied.

Strategies for pollen avoidance can help reduce exposure, but it is difficult to achieve complete avoidance. Use of air conditioning is an effective intervention that can filter out pollen from indoor spaces. Avoiding prolonged outdoor exposure during high pollen counts and bathing/changing clothes after pollen exposure can also be helpful.

The role of climate change and allergies is a broader issue, ultimately highlighting the need to curb fossil fuel combustion and invest in clean energy. Some studies have shown that increasing green spaces within urban environments can help reduce allergy and asthma symptoms.[129] However, some studies have shown increased association with green space and allergen sensitization.[130] Further studies are needed to clarify how to develop interventions that will lead to a positive impact on the health of communities.

Outdoor Mold

Outdoor mold spore counts are increased with warmer temperatures and humidity. The effects of climate change can lead to increased exposure to mold outdoors (through weather change) and indoors as a result of extreme weather events such hurricanes and flooding, leading to more opportunity for indoor dampness. Warmer weather associated with climate change is contributing to rising sea levels worldwide, which in turn play a role in extreme weather events such as flooding. Outdoor mold exposure has been linked to asthma morbidity. In an Australian study, outdoor mold exposure was associated with child asthma hospitalizations.[125]

Mitigating exposure to outdoor mold spores can be challenging similar to pollen avoidance strategies. However, knowledge of individual mold sensitization may help with risk stratification among individuals with asthma and help guide who may benefit most from strict outdoor avoidance during high mold spore counts and associated weather conditions. Remediation of indoor mold is expensive, and the projected likely increase in prevalence of indoor dampness related to climate change will pose another challenge in optimizing avoidance measures to reduce asthma morbidity. This will likely have a disproportionately larger impact on communities with older homes, restricted access to maintenance capabilities, and rental properties, thus adding to the health disparities in urban environments and communities of lower socioeconomic status.

OTHER ITEMS COMPRISING EXPOSOME

Antibiotics

As previously mentioned in the microbiome section of this article, exposures to consider both prenatally and postnatally that may contribute to asthma as part of the exposome include medications such as antibiotics. In the United States, more than 12% of clinic visits result in a prescription for an antibiotic, and 30% of those prescriptions may be unnecessary.[131,132] Antibiotic exposure during infancy has been shown to be a risk factor for the diagnosis of asthma, as shown in a study in Canada evaluating 213, 661 mother-child dyads, which found that 36.8% of children were prenatally exposed to antibiotics, and

10.1% developed asthma. This antibiotic exposure was associated with increased risk of asthma (hazard ratio 1.23 [1.20–1.27]). A relation to number of antibiotic courses with increased risk of asthma was also found.[132]

Studies have demonstrated an increased association of asthma in children with the prescribing and dispensation of antibiotics to mothers during pregnancy. However, there also appears to be an effect before pregnancy or after birth when mothers are lactating or afterward. These associations of antibiotic use and development of asthma (with odds ratio [OR] of at least 1.23), although present in larger cohort studies, may have a causal role or may be related to other confounding factors that increase the propensity of a child having asthma. Confounders are obvious, such that the mother may have a predisposition to asthma, may have a trend for multiple infections warranting treatment and thus are already compromised, and/or that alteration of the mother's microbiome may lead to an intrinsic predisposition toward asthma. However, in many cases, even with such predispositions, analyses still demonstrate that antibiotic exposure has been a risk factor.[133–135]

Although causal association with alteration of immune function may be part of this association, familial factors such as genetic predisposition (examined by sibling controls), family propensity for infection, and other individual factors such as nutrition (vitamin D), environmental, or genetics are likely at play.[136,137] Finally, health care utilization patterns may be influencing these associations.[137] In summary, although the precise mechanism of these associations is not fully clear, judicious use of antibiotics during this period, as in other times, appears to be warranted.

Related factors of the exposome, such as diet/nutrition and exposures related to occupation and hobbies, have been indirectly or briefly touched upon in this article. These factors should be explored and taken into consideration during the evaluation and management of such patients. **Table 1** lists occupations that need to be considered as potential risks for initiating or enhancing asthma.

Table 1
Occupations at high risk for influencing respiratory health

Occupation	Trigger
Painters, roofers, insulators	Isocyanates
Famers, agricultural workers	Animal proteins, plants, fungicides
Cleaners	Amines
Bakers	Flours and cereals
Laboratory workers	Animal proteins, chemical exposure (eg, formaldehyde or glutaraldehyde)
Factory workers (manufacturing facilities of paint, plastics, epoxy resins)	Anhydrides
Carpenters	Wood dust
Welders and metal workers	Metals
Hair dressers	Chemicals in hair products, dyes
Health professionals	Latex, biocides, acrylates

MEDICAL COMMUNITY CALL TO ACTION

The implications of the science of exposome, environment, and asthma are immense. The World Health Organization (WHO) and Health Effects Institute (HEI) and Lancet report on climate change estimate that by 2016, approximately 125 million additional vulnerable adults will be exposed to heat waves, putting them at risk for additional disease and premature death.[13] Societies are evaluating the evidence, valuing the science, and speaking up to have a concerted effort to address these threats.[138,139] Ambient air pollution caused 3 million premature deaths from overlapping effects of increased greenhouse gas emissions and air pollution. This is particularly relevant to respiratory health, as future projections estimate 130 million people (half of the global population) will have allergic disease by 2050.[140] There have been more accelerated changes in climate in the last 40 years, and it has been suggested that a feasible goal, that of limiting the temperature rise to 2° above preindustrial times, would prevent the accelerated consequences on ecology, human access to food, and health.[140]

Professional Medical Societies Are Recognizing This to Be a Problem

Although there is a growing awareness among the health care community, environmental factors and climate change have been slow to become part of the partnerships between patients and health care providers. However, professional societies and public health advocates have become more vocal and proactive with statements that highlight the known epidemiologic and pathophysiologic rationale and mechanisms of air quality/environment and health.

Experts agree upon the need to increase public recognition and awareness of this issue as well as educate regarding early warning signs to mitigate the effects on vulnerable populations. To do this, coordinated efforts are necessary among communities of clinicians to engage in, advocate, and influence public policy. Development and funding of climate change research centers are essential.[12,13]

Populations at Disproportionate Risk for Air Pollution-Related Asthma Morbidity

It is well established that these effects target people who are young, older, and with chronic medical problems. Studies globally have demonstrated that the population older than 65 years has a greater risk of death.[99,101] Meanwhile in many instances, children appear to be at higher susceptibility compared with adults for emergency department visits for asthma.[11,84] These effects also disproportionately affect those in minority and impoverished communities. Heat waves affect certain populations preferentially, include older individuals, children, laborers, certain ethnic or racial groups, and individuals of low socioeconomic status. These are additive risk factors to air pollution, high humidity, and lack of air conditioning.[9]

There are different levels of risk of mortality and morbidity from air pollution depending on baseline chronic conditions and other factors. The elderly population worldwide is at risk, varying from groups greater than 65 or greater than 75 years old, with higher rates of death in association with particulate matter in the United States (6 cities), South America, and Europe.[99] Ozone and total suspended particles were also associated with mortality in the Netherlands.[141] These associations with mortality remain temporally associated, as rates decrease when air pollution levels become lower again.[142] Children are at risk with exposures to particulate matter, sulfur and nitrogen dioxides, and diesel. These pollutants have been associated with reduced lung function parameters, asthma, and respiratory symptoms. Ozone, nitrogen dioxide, particulate matter, and sulfur dioxide are associated with asthma attacks.[80] Therefore, health effects from short- and longer-term air pollution exposures likely are derived from oxidative stress and immune dysfunction. Those of lower socioeconomic status are at heightened risk because of other usual additional risk factors, home environment/geographic conditions, living in areas of higher pollution, access to care, and related health factors such as malnutrition and smoking.[143]

Importantly, it should be noted that as the exact mechanisms, pace of change, and effects on human respiratory health are debated, regardless of which scientific and mathematical models are used, having policies that address and mitigate climate change consistently indicates that a large number of deaths would be avoided as compared to a scenario where no policy is implemented at all.[144]

SUMMARY

Knowledge of intrinsic and extrinsic factors that predispose people to develop asthma is growing. It is also clear that there is a unique interplay of endosome and exposome in the pathophysiology of respiratory diseases from allergies and asthma. Both indoor and outdoor environments play a role in pathogenesis via levels and duration of exposure, with genetic susceptibility as a crucial factor that alters the initiation and trajectory of a common conditions. The scientific evidence is clear with these known associations. To some degree these exposures can be reduced via a collaborative multinational and global intent to do so. Members of the medical community must understand these factors to better care for patients and potentially prevent future disease from occurring or guard patients with means to mitigate their risks for worsening asthma.

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